Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
January 29, 2013
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center
(Rm. 1503), Silver Spring, MD

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for January 29, 2013 Meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration were approved on March 27, 2013.

I certify that I attended the January 29, 2013 meeting of the Pulmonary-Allergy Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, Pharm.D.
Designated Federal Officer
Pulmonary-Allergy Drugs Advisory Committee (PADAC)

_____/s/_____
David Jacoby, M.D.
Chairperson, PADAC

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Center for Drug Evaluation and Research met on January 29, 2013 from 8 a.m. to 5 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, Boehringer Ingelheim. The meeting was called to order by David Jacoby, MD (Committee Chairperson); the conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 120 persons in attendance. There was one (1) speaker for the Open Public Hearing session.

Issue: The committee discussed the new drug application (NDA) 203108, for olodaterol (proposed trade name Striverdi Respimat) metered dose inhaler, sponsored by Boehringer Ingelheim, for the proposed indication of long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Attendance:

Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting): Kathryn Blake, PharmD, Paul A. Greenberger, MD, David B. Jacoby, MD (Chairperson), Rodney Mullins (Consumer Representative), Kelly Dean Stone, MD, PhD, Peter B. Terry, MD

Pulmonary-Allergy Drugs Advisory Committee Members Not Present:
Steven D. Shapiro, MD, Judith Voynow, MD

Temporary Members (Voting):
Bill T. Ameredes, PhD, Mark Brantly, MD, William J. Calhoun, MD, Paula G. Carvalho, MD, John E. Connett, PhD, Edna Fiore (Patient Representative), Michelle S. Harkins, MD, FCCP, Amy H. Herring, ScD, John Hoidal, MD, Udho Thadani, MD, MRCP, FRCPC, FACC, FAHA, James M. Tracy, DO

Industry Representative to the Pulmonary-Allergy Drugs Advisory Committee (Non-Voting): Howard M. Druce, MD (Industry Representative)

FDA Participants (Non-Voting):
Curtis Rosebraugh, MD, MPH, Badrul Chowdhury, MD, PhD, Robert Lim, MD, Robert Abugov, PhD, Theresa Michele, MD

Designated Federal Officer:
Cindy Hong, PharmD

Open Public Hearing Speaker:
Vlady Rozenbaum, PhD

The agenda was as follows:

Call to Order	**David B. Jacoby, MD**

Introduction of Committee	Chairperson, Pulmonary-Allergy Drugs Advisory Committee (PADAC)
Conflict of Interest Statement	**Cindy Hong, PharmD** Designated Federal Officer, PADAC
Opening Remarks	**Theresa Michele, MD** Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), Office of Drug Evaluation II (ODE-II), Office of New Drugs (OND), CDER, FDA
Sponsor Presentations	**Boehringer Ingelheim**
Introduction	**Sabine Luik, MD** Head of US Medicine and Regulatory Affairs Boehringer Ingelheim
COPD Disease Background	**Richard Casaburi, MD, PhD** Professor of Medicine UCLA School of Medicine Medical Director, Rehabilitation Clinical Trials Center Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Olodaterol Clinical Program	**Alan Hamilton, PhD** Senior Clinical Program Leader Boehringer Ingelheim
Safety and Risk Management of Olodaterol for COPD	**Bernd Disse, MD, PhD** Head, Therapeutic Area Respiratory Diseases Boehringer Ingelheim
Clinical Summary and Perspective on the Use of Olodaterol for Patients with COPD Clarifying Questions to the Presenters	**Richard Casaburi, MD, PhD**
FDA Presentations	
Overview of the Clinical Program	**Robert Lim, MD** Clinical Reviewer DPARP, ODE-II, CDER, FDA
Statistical Review of Efficacy	**Robert Abugov, PhD**

Statistical Reviewer
Division of Biostatistics II (DB-II)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS),
CDER, FDA

Clinical Review of Efficacy, Safety, Risk/Benefit	**Robert Lim, MD**
Clarifying Questions to the Presenters	
Open Public Hearing	
Charge to the Committee	**Theresa Michele, MD**
Questions to the Committee and Committee Discussion	
Questions to the Committee and Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION**: Discuss the bronchodilator efficacy data for olodaterol.

   Members of the committee agreed that olodaterol was effective as a bronchodilator based on FEV1. One committee member stated that, while there was an effect on FEV1 at 12 and 24 weeks, he would have preferred that the effect had been clearly maintained over the 48 week trial duration. He also expressed concern that with respect to 'hard endpoints' (i.e. exacerbations), the data were not going in the right direction.

   Other members commented that it's difficult to see improvements in 'hard endpoints' when olodaterol is added to baseline therapy. Members also commented that patients can benefit from long-term bronchodilation without necessarily seeing an improvement in exacerbations.

   A few members expressed concerns over the small number of African Americans and Hispanics included in the trials. Boehringer Ingelheim clarified that these groups were not excluded as a part of the trial design and that the percentages enrolled were typical of a COPD development program.

2. **DISCUSSION**: Discuss the overall safety profile of olodaterol.

   Overall, members felt that the safety profile was similar to other LABAs. However, there was some concern regarding the occurrence of lung related malignant neoplasms. One member noted that it is conceivable that something about olodaterol could act to promote neoplasms. Several members of the committee thought that some form of post-marketing surveillance was warranted. One committee member also commented that more safety data in non-white populations would have been ideal.

3. **DISCUSSION**: Discuss the proposed exercise claims for olodaterol, including the following:
    a) design of trials (e.g. duration, timing of medication and exercise testing)
    b) minimum clinically important difference for exercise endurance, and
    c) increased inspiratory capacity (IC) during exercise

    Overall, the committee felt that exercise tolerance is important to patients with COPD and is thus a valuable endpoint to capture in clinical trials. However, the committee felt that, while the BI exercise trials were a good starting point, there were issues with the interpretation of the clinical meaningfulness of the data. Members commented that the exercise testing was only performed at peak olodaterol effect and not at trough. Some members stated that more data throughout the dosing interval would have been ideal, as different patients may be more or less active during portions of the dosing interval. One member also commented that the improvements seen in the exercise testing may have been due to a training effect rather than a drug effect. With regard to minimum clinically important difference (MCID)for exercise tolerance, there was no consensus among the committee members as to what it should be. However, some members stated that for any improvement to be meaningful, it should translate into improvements in activities of daily living. Little comment was made on IC; however, some felt that it was too early to link it to symptom relief. It was also noted by the committee that developing an FDA guidance on exercise testing would be beneficial for the future, and a scientific consensus meeting on the topic may be helpful.

4. **VOTE**: Considering the totality of the data, has olodaterol demonstrated substantial evidence of efficacy for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema?
    a) If not, what further data should be obtained?

    YES: 15 **NO:** 1 **ABSTAIN:** 1

    Members who voted "YES" noted that the sponsor had designed rigorous trials and had shown significant evidence of efficacy as a bronchodilator. It was also noted that there was a dose- response relationship and the once daily dosing is preferable for patients. Members mentioned that the two primary end points were achieved.

    The member who voted "No" noted that he could not support an efficacy claim in the broad population based on trials that did not include adequate representation of United States ethnic minority groups.

    One member abstained from voting because he would have liked to see longer term data and improvements in 'hard endpoints'.

5. **VOTE**: Is the safety profile of olodaterol adequate for approval for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema?
    a) If not, what further data should be obtained?

    YES: 15 **NO:** 1 **ABSTAIN:** 1

The members voting "YES" noted that the safety data show no concerning safety signal and that safety was adequately demonstrated. Some members noted the need for post-marketing surveillance for lung related malignant neoplasms, especially small cell carcinomona. One member also wanted additional safety data in African-American patients.

The member who voted "NO" commented that he could not support safety as the data were derived from a primarily white patient population. He was concerned that the safety profile predicted by the study population may not be applicable to the non-white population.

One member abstained from voting on this question as he abstained from the previous question, but he had no specific safety issues.

6. **VOTE**: Based on the information included in the briefing materials and presentations, has the applicant provided sufficient efficacy and safety data to support marketing of olodaterol inhalation solution for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema?
    a) If not, what further data should be obtained?

    YES: 15 **NO:** 1 **ABSTAIN:** 1

    The members voting "YES" commented that the sponsor demonstrated efficacy and safety. Some members noted that while olodaterol may be effective as a bronchodilator, the data were not supportive of an exercise tolerance claim.

    The member who voted "NO" commented that a lay person may make false assumptions about the capabilities of the drug in the general population.

    One member abstained since he also abstained from the previous two questions, but noted that the drug does function as a bronchodilator, but he would like to see some improvements in 'hard endpoints'

(Please see official transcript for details.)

The meeting adjourned at approximately 3:18 p.m.